Summary Minutes of the for the Joint Meeting of the Arthritis Advisory Committee and the Drug Safety and Risk Management Advisory Committee May 12, 2010

Location: Hilton Silver Spring/Washington D.C., The Ballrooms, 8727 Colesville Road, Silver Spring, Maryland.

All external requests for the meeting transcripts should be submitted to the CDER, Freedom of Information office.

A verbatim transcript will be available in approximately two-four weeks, sent to the Division and posted on the FDA website at: http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisDrugsAdvisoryCommittee/ucm203434.htm

These summary minutes for May 12, 2010 Joint Meeting of the Arthritis Advisory Committee and the Drug Safety and Risk Management Advisory Committee were approved on May 28, 2010.

I certify that I attended the May 12, 2010, Joint Meeting of the Arthritis Advisory Committee and the Drug Safety and Risk Management Advisory Committee and that these minutes accurately reflect what transpired.

_____/s/_____
Anuja Patel, M.P.H.
Designated Federal Official, ACPS-CP

_____/s/_____
Kathleen O'Neil, M.D.
Committee Chair

Summary Minutes
Meeting of the Joint Meeting of the Arthritis Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee

May 12, 2010

The Arthritis Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee met on May 12, 2010 at the Hilton Silver Spring/Washington D.C., The Ballrooms, 8727 Colesville Road, Silver Spring, Maryland. Prior to the meeting, members and invited consultants were provided copies of the background material from the FDA. The meeting was called to order by Kathleen O'Neil, M.D. (Committee Chair); the conflict of interest statement was read into the record by Anuja Patel, M.P.H. (Designated Federal Official). There were approximately 100 persons in attendance. There were two (2) speakers for the Open Public Hearing session.

Issue: On May 12, 2010, the committees discussed new drug application (NDA) 22-478, naproxcinod 375 milligram capsule, sponsored by NicOx S.A., a non-steroidal anti-inflammatory drug (NSAID) product indicated for the treatment of the signs and symptoms of osteoarthritis.

Attendance:
Arthritis Drug Advisory Committee Members Present (Voting):
Diane Aronson *(Consumer Representative)*, David Blumenthal, M.D., Robert Kerns, Ph.D., Ted Mikuls, M.D., MSPH, Nancy Olsen, M.D., Christy Sandborg, M.D., Kathleen O'Neil, M.D. *(Chair)*

Drug Safety and Risk Management Drug Advisory Committee Members Present (Voting):
Sidney Wolfe, M.D. *(Consumer Representative,)*

Drug Safety and Risk Management Drug Advisory Committee Temporary Members (Voting):
William Cooper, M.D., M.P.H., Jodi B. Segal, M.D., M.P.H., T. Mark Woods, Pharm. D., FASHP, BCPS, William Greene, Pharm.D.

Non-voting Participants:
Mark Fletcher, M.D. *(Arthritis Advisory Committee Industry Representative)*
D. Bruce Burlington, M.D. *(Drug Safety and Risk Management Advisory Committee Industry Representative)*

Temporary Voting Members:
William O. Brackney *(Patient Representative)*, Dennis Dixon, Ph.D., Michael Domanski, M.D., Robert Harrington, M.D., Denis McCarthy, M.D., Maria Sjogren, M.D., M.P.H., FACP

Arthritis Advisory Committee Members Not Present:
Robert Stine, Ph.D.

Drug Safety and Risk Management Advisory Committee Members Not Present:
Sander Greenland. Dr.P.H., Susan Heckbert, M.D., Ph.D., Judith Kramer, M.D., M.S., Elaine Morrato, Dr. P.H., Allen Vaida, Pharm.D., FASHP, Lewis Nelson, M.D.

FDA Participants (Non-Voting):
Curtis J. Rosebraugh, M.D.**,** Bob Rappaport, M.D.**,** Sharon Hertz, M.D.**,** Robert Shibuya, M.D.

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May 12, 2010

Continued-
Open Public Hearing Speakers:
1. Seth Ginsberg
2. Vincent Friedewald, M.D.

The agenda was as follows:

Call to Order	Kathleen O'Neil, MD Chair, AAC
Conflict of Interest Statement	Anuja Patel, MPH Designated Federal Officer
Opening Remarks	Robert Shibuya, MD Clinical Team Leader Division of Anesthesia and Analgesia Products (DAAP), CDER/FDA
Sponsor Presentations:	
Introduction	**Elizabeth Robinson, PhD** President, NicOx Research Institute Srl
Rationale for Development of Naproxcinod	**Marc Hochberg, MD** Professor of Medicine Head, Division of Rheumatology and Clinical Immunology University of Maryland School of Medicine
Clinical Efficacy and Safety	**Pascal Pfister, MD, MFPM** NicOx, Chief Scientific Officer Head of Research & Development
Blood Pressure Overview	**William White, MD** Professor and Chief Division of Hypertension and Clinical Pharmacology, Calhoun Cardiology Center, University of Connecticut School of Medicine, Farmington, Connecticut
Importance of SBP Levels in Patients with OA	**Michael Weber, MD** Professor of Medicine SUNY Downstate Medical College of Medicine Brooklyn, New York
Benefit Risk of Naproxcinod	**Marc Hochberg, MD**

Continued-

FDA Presentations:

Naproxcinod: FDA Efficacy and Safety Review	**Jacqueline Spaulding, MD, MPH** Medical Officer DAAP, CDER/FDA **Feng Li, PhD** Biometrics Reviewer Office of Biostatistics CDER/FDA
Cardiovascular Summary Review	**Suchitra Balakrishnan, MD, PhD** Medical Officer Division of Cardiovascular and Renal Products CDER/FDA
Review of Endoscopy Studies	**Wen-Yi Gao, MD, PhD** Medical Officer Division of Gastroenterology Products CDER/FDA
Pharmacokinetics of Naproxcinod and Naproxen	**Wei Qiu, PhD** Clinical Pharmacology Reviewer Office of Clinical Pharmacology CDER/FDA
Lunch Break	
Open Public Hearing	
Committee Discussion and Voting	

Continued-

Committee voting, discussion, and recommendations:

Questions to the Committee:

1. Based on the results of the studies assessing the efficacy of naproxcinod and naproxen:

    a. Is there evidence that naproxcinod is as effective as naproxen?

    Overall, the Committee agreed that data presented by the sponsor only indicated that naproxcinod was more efficacious than placebo. The committee strongly felt that data presented on the two noninferiority analyses was marginal, indicating that naproxcinod MAY be as effective as naproxen. [The FDA clarified the question by proposing that if the committee agrees that a standard of "likely as effective as naproxen" is reasonably acceptable, then FDA could consider this recommendation in its potential for approval. The FDA requested discussion by the committee on potential issues with naproxcinod based on the data provided.] Overall, the committee expressed concern with unknown potential safety risks with naproxcinod's nitric oxide-donating component, as panel members felt the sponsor did not provide data to address such potential safety risks including GI bleeding and decreased harm associated with hypertension. The committee felt that safety demonstrated by the studies providing" reasonable" efficacy was underpowered. The committee agreed that the sponsor did not provide enough data regarding gastrointestinal (GI) benefit. The Committee further debated on this question with regards to naproxcinod being as effective as naproxen and the question was not resolved based on the data presented.

    Please see transcript for complete details

    b. Is the applicant's choice of a noninferiority margin of 70% of the treatment effect size appropriate to determine that efficacy of the two products is similar?

    The Committee felt that it could not provide sufficient recommendation based upon the data presented.

    Please see transcript for complete details

        i. If not, what would be an acceptable noninferiority margin for this situation?

        Please see Question 1b.

    c. Do you think that the reduced relative bioavailability may have been a factor in failure to demonstrate noninferiority?

    The panel agreed that the reduced relative bioavailability was a factor in the failure to demonstrate noninferiority based on the statistical data presented since there was a 25% drop out rate in most of the studies.
    Please see transcript for complete details

2. The data presented demonstrate that there is an average difference in blood pressure measurements, but no sustained effect throughout the dosing interval. Discuss whether the blood pressure effects of naproxcinod are likely to improve cardiovascular outcomes in patients requiring long-term treatment with naproxen.

Question 2 Continued-

a. Will the lack of sustained effect throughout the dosing interval result in a failure to reduce the risk for adverse cardiovascular outcomes?

The committee reiterated that sufficient data was not presented to effectively extrapolate an answer to this question. The committee suggested that long-term studies, collected over time (an example of at least five years was suggested), are needed to allow appropriate extrapolation.
Please see transcript for complete details

b. Does the peak effect on blood pressure pose a potential safety concern for patients?
The committee again agreed that insufficient data has been provided to know whether data can be extrapolated to the larger population. A long-term study would be needed to address this question.

Please see transcript for complete details

3. The data presented describe an effect on the occurrence of erosions, but were not of adequate design to assess an effect on the occurrence of ulcers. Discuss whether the effects of naproxcinod to reduce the number of erosions in the absence of demonstrating an effect on gastric ulcers has clinical value in patients requiring long-term treatment with naproxen.
Overall, the committee agreed that data presented was unclear for several reasons, one being that gastric acid inhibitors were allowed. [Also, since the sponsor removed its GI claim, the FDA asked the committee for suggestions on possible studies regarding (GI) outcomes.] Several members suggested that the outcome which ***should have*** *been evaluated is bleeding. One member suggested that evaluation of gastropathies with regards to non-steroidal anti-inflammatory drugs (NSAIDs)-induced bleeds should not be inspected by FDA, as NSAIDs induce weak bleeds and may not be the correct signal. The committee agreed that there is a signal and the correct signal needs to be identified and studied with long-term clinical end points.*

Please see transcript for complete details

a. Are the studies submitted adequate to assess whether there is a meaningful effect on GI outcomes?

This question was answered in the overall discussion of Question 3.

b. If not, what changes should be made for future studies?
This question was answered in the overall discussion of Question 3.

c. Can the effect on GI outcomes be explained by the lower relative exposure to naproxen that result from dosing with naproxcinod?

This question was answered in the overall discussion of Question 3.

4. Please vote on whether naproxcinod should be approved for the indication of the treatment of the signs and symptoms of osteoarthritis, taking into account the efficacy, pharmacokinetic and safety findings. (YES/NO/ABSTAIN)

Yes= 1 *No= 16* *Abstain= 1*

Please see transcript for complete details

Question 4 Continued-

A follow up question was added to Question 4:

If the vote is no, what additional data would the committee like the sponsor to provide in order to move forward to a possible approval in the future?

Overall, the committee was enthusiastic regarding the potential for naproxcinod but needed additional data. The committee suggested more studies in high risk populations, including elderly, individuals with pre-existing cardiovascular risk factors, and GI risk factors be performed. The committee also suggested additional studies be performed on naproxcinod's interaction with other agents, particularly those that are vasoactive, platelet-active, or GI related. The committee also advised the sponsor to look at anticoagulant agents that may impact the outcome in the target population. The committee also requested additional data on the GI safety effect of the drug, specifically with regards to bleeding. The committee was concerned with hypotension in the elderly population as well as in patients on vasoactive drugs. The committee also requested additional data regarding cardiovacular effects as a primary marker of the drug as opposed to using blood pressure as a surrogate marker. The panel requested additional short and long-term blood pressure studies because of their concern on blood pressure changes over time. The panel suggested that renal outcomes need to be addressed in future studies.

Please see transcript for additional details

The meeting adjourned at 3:30 p.m.